



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| <b>(54) Title:</b> USE OF 5-HT <sub>4</sub> MODULATORS FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF THE BLADDER DISEASES<br><br><b>(57) Abstract</b><br><br>A compound which acts as an antagonist at 5-HT <sub>4</sub> receptors is of potential use in the treatment of conditions associated with bladder hypersensitivity, such as urinary incontinence, which is often associated with irritable bowel syndrome (IBS) and a compound which acts as an agonist at 5-HT <sub>4</sub> receptors is of potential use in the treatment of conditions associated with a poorly functioning bladder, such as urinary bladder hypoactivity following prostatectomy.  |           |   |

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Use of 5-HT<sub>4</sub> modulators for the manufacture of a  
medicament for the treatment of the bladder diseases

5 This invention relates to treatment of conditions associated with bladder hypersensitivity, and conditions associated with a poorly functioning bladder.

European Journal of Pharmacology 146 (1988), 187-188, and Naunyn-Schmiedeberg's Arch. Pharmacol. (1989) 340:403-410, describe a non classical 5-hydroxytryptamine receptor, now designated the 5-HT<sub>4</sub> receptor, and that tropisetron (ICS 205-930), which is also a 5-HT<sub>3</sub> receptor antagonist, acts as an antagonist at this receptor and metoclopramide is an agonist at this receptor.

15 WO 91/16045 (SmithKline and French Laboratories Limited) describes the use of cardiac 5-HT<sub>4</sub> receptor antagonists in the treatment of atrial arrhythmias and stroke.

20 Metoclopramide has been shown to be effective in treating a poorly functioning bladder, (Scand. J. Urology and Nephrology, 13:79-82 (1979) but this has not been specifically linked to any known action of metoclopramide.

25 There are reports in the literature of 5-HT<sub>4</sub> receptors potentiating contractions in human bladder (Br. J. Pharmacol, 61, 115P) and inhibiting contractions in monkey bladder (2nd International Symposium on Serotonin, Houston, September 1992, page 86).

30 We have now discovered that a compound which acts as an antagonist at 5-HT<sub>4</sub> receptors is of potential use in the treatment of conditions associated with bladder hypersensitivity, such as urinary incontinence, which is often associated with irritable bowel syndrome (IBS) and a compound which acts as an agonist at 5-HT<sub>4</sub> receptors is of potential use in the treatment of conditions associated with a poorly functioning bladder, such as urinary bladder hypoactivity following prostatectomy. When used herein the term '5-HT<sub>4</sub> modulator' is used to denote antagonists and agonists.

35 The invention therefore provides a method for the treatment and/or prophylaxis of conditions associated with bladder hypersensitivity and conditions associated with a poorly functioning bladder in mammals, including

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humans, which method comprises administering to the mammal in need of such treatment and/or prophylaxis, an effective and/or prophylactic amount of a 5-HT<sub>4</sub> modulator.

- 5 5-HT<sub>4</sub> modulators may be identified according to standard methods, such as those described hereinafter, and that described in Naunyn-Schmiedeberg's Arch Pharmacol. 342, 619-622.

- 10 Examples of 5-HT<sub>4</sub> receptor antagonists include ICS 205-930 (tropisetron - Sandoz), R 50 595 (Janssen), which is described in FR 76530 and Eur.J. Pharmacol., 181 119-125 (1990), and SDZ 205-557, which is described by K.H. Buchheit and R. Gamse in Naunyn-Schmiedeberg's Arch. Pharmacol., 343 (Suppl.), R101 (1991). DAU 6285 (Naunyn-Schmiedeberg's Arch. Pharmacol., 345; 264-269 (1992) and RS 23597-190 (Syntex - British  
15 Pharmacology Society Meeting, September 1992).

- EP-A-501322 (Glaxo Group Limited) describes indole derivatives having 5-HT<sub>4</sub> receptor antagonist activity and reports 5-HT<sub>4</sub> receptors are believed to be associated with conditions involving *inter alia* the urinary tract (e.g.  
20 urinary incontinence).

Examples of 5-HT<sub>4</sub> receptor agonists include cisapride, renzapride and zacopride.

- 25 In one aspect, the 5-HT<sub>4</sub> modulator is more potent at 5-HT<sub>4</sub> receptors than at 5-HT<sub>3</sub> receptors.

- Preferably, the 5-HT<sub>4</sub> modulator is in substantially pure pharmaceutically acceptable form.

- 30 The administration of the 5-HT<sub>4</sub> modulator may be by way of oral, sublingual, transdermal or parenteral administration.

- 35 An amount effective to treat the disorder hereinbefore described depends on the usual factors such as the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose will normally contain 0.1 to 50 mg for example 0.5 to 10 mg, of the 5-HT<sub>4</sub> modulator. Unit doses will normally be administered once or more than once a day, for example 2, 3,

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or 4 times a day, more usually 1 to 3 times a day, such that the total daily dose is normally in the range, for a 70 kg adult of 0.1 to 50 mg, for example 0.1 to 5 mg, that is in the range of approximately 0.001 to 1 mg/kg/day, more usually 0.005 to 0.2 mg/kg/day.

5

For oral or parenteral administration, it is greatly preferred that the 5-HT<sub>4</sub> modulator is administered in the form of a unit-dose composition, such as a unit dose oral or parenteral composition.

- 10 Such compositions are prepared by admixture and are suitably adapted for oral or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable and infusable solutions or suspensions or suppositories.

15

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tableting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known  
20 methods in the art.

- Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for  
25 example, magnesium stearate. Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate.

- These solid oral compositions may be prepared by conventional methods of blending, filling or tableting. Repeated blending operations may be used to  
30 distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

- Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as  
35 a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or

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hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral formulations also include conventional sustained release formulations, such as tablets or granules having an enteric coating.

For parenteral administration, fluid unit dose forms are prepared containing the 5-HT<sub>4</sub> modulator and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved.

Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

As is common practice, the compositions will usually be accompanied by written or printed directions for use in the treatment concerned.

The present invention also provides the use of a 5-HT<sub>4</sub> modulator in the manufacture of a medicament for use in the treatment and/or prophylaxis of conditions associated with a poorly functioning bladder and bladder hypersensitivity. Such treatment and/or prophylaxis may be carried out as hereinbefore described.

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The present invention further provides a pharmaceutical composition for use in the treatment and/or prophylaxis of conditions associated with a poorly functioning bladder and bladder hypersensitivity, which comprises a 5-HT<sub>4</sub> modulator, and a pharmaceutically acceptable carrier. Such compositions  
5 may be prepared in the manner as hereinbefore described.

#### 5-HT<sub>4</sub> modulator activity

10

##### 1) Guinea pig colon

Male guinea-pigs, weighing 250-400g are used. Longitudinal muscle-myenteric plexus preparations, approximately 3cm long, are obtained from  
15 the distal colon region. These are suspended under a 0.5g load in isolated tissue baths containing Krebs solution bubbled with 5% CO<sub>2</sub> in O<sub>2</sub> and maintained at 37°C. In all experiments, the Krebs solution also contains methiothepin 10<sup>-7</sup>M and granisetron 10<sup>-6</sup>M to block effects at 5-HT<sub>1</sub>, 5-HT<sub>2</sub> and 5-HT<sub>3</sub> receptors.

20

After construction of a simple concentration-response curve with 5-HT, using 30s contact times and a 15min dosing cycle, a concentration of 5-HT is selected so as to obtain a contraction of the muscle approximately 40-70% maximum (10<sup>-9</sup>M approx). The tissue is then alternately dosed every 15min  
25 with this concentration of 5-HT and then with an approximately equi-effective concentration of the nicotine receptor stimulant, dimethylphenylpiperazinium (DMPP). After obtaining consistent responses to both 5-HT and DMPP, increasing concentrations of a putative 5-HT<sub>4</sub> modulator are then added to the bathing solution. The effects of this compound are then determined as a  
30 percentage reduction of the contractions evoked by 5-HT or by DMPP.

From this data, IC<sub>50</sub> values are determined, being defined as the concentration of antagonist or agonist which reduces or increases the contraction by 50%. A compound which reduces the response to 5-HT but  
35 not to DMPP is believed to act as a 5-HT<sub>4</sub> receptor antagonist and a compound which increases the response to 5-HT but not to DMPP is believed to act as a 5-HT<sub>4</sub> receptor agonist.

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**2) Rat oesophagus**

Rat oesophageal tunica muscularis mucosae is set up according to Baxter *et al.* Naunyn-Schmiedeberg's Arch. Pharmacol., 343, 439-446 (1991). The  
5 inner smooth muscle tube of the muscularis mucosae is isolated and  
mounted for isometric tension recording in oxygenated (95% O<sub>2</sub>/5% CO<sub>2</sub>)  
Tyrodes solution at 37°C. All experiments are performed in pargyline pre-  
treated preparations (100µM for 15 min followed by washout) and in the  
presence of cocaine (30µM). Relaxant responses to 5-HT are obtained after  
10 pre-contracting the oesophagus tissue with carbachol (3µM).

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**Claims**

1. A method for the treatment and/or prophylaxis of conditions associated with bladder hypersensitivity and conditions associated with a poorly functioning bladder in mammals, including humans, which method comprises administering to the mammal in need of such treatment and/or prophylaxis, an effective and/or prophylactic amount of a 5-HT<sub>4</sub> modulator.
2. The use of a 5-HT<sub>4</sub> modulator in the manufacture of a medicament for use in the treatment and/or prophylaxis of conditions associated with a poorly functioning bladder and bladder hypersensitivity.
3. A pharmaceutical composition for use in the treatment and/or prophylaxis of conditions associated with a poorly functioning bladder and bladder hypersensitivity, which comprises a 5-HT<sub>4</sub> modulator, and a pharmaceutically acceptable carrier.
4. A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT<sub>4</sub> modulator is a 5-HT<sub>4</sub> receptor antagonist.
5. A method, use or composition according to claim 4 for the treatment of urinary incontinence.
6. A method, use or composition according to claim 5 for the treatment of urinary incontinence associated with irritable bowel syndrome.
7. A method, use or composition according to claim 4, 5 or 6 wherein 5-HT<sub>4</sub> receptor antagonist is R 50 595, SDZ 205-557, DAU 6285, RS 23597-190 or a compound described in relation to EP-A-501322 (Glaxo Group Limited).
8. A method, use or composition according to claim 1, 2 or 3 wherein the 5-HT<sub>4</sub> modulator is a 5-HT<sub>4</sub> receptor agonist.
9. A method, use or composition according to claim 8 for the treatment of urinary bladder hypoactivity following prostatectomy.

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10. A method, use or composition according to claim 8 or 9 wherein 5-HT<sub>4</sub> receptor agonist is cisapride, renzapride or zacopride.

## International Application No.

**PCT/GB 92/02376**

Form PCT/TSA/210 (second sheet) (January 1985)

| III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET) |  | Relevant to Claim No. |
|--|--|-----------------------|
| Category *   | Citation of Document, with indication, where appropriate, of the relevant passages   |                       |
| X  | <p>PARAPLEGIA<br/>vol. 26, no. 3, 1988,<br/>pages 159 - 161;<br/>G.H. DE GROOT ET AL.: 'Effects of cisapride on<br/>constipation due to neurological lesion'<br/>see discussion<br/>see abstract</p> <p>---</p>  | 1-3,8-10              |
| X  | <p>ACTA BELG. MED. PHYS.<br/>vol. 12, no. 3, 1989,<br/>pages 81 - 88;<br/>P.HANSON ET AL.: 'Effet du cisapride sur les<br/>vessies neurologiques'<br/>see conclusions</p> <p>---</p>   | 1-3,8-10              |
| P,X  | <p>DRUG. DEV. RES.<br/>vol. 27, no. 4, 1992,<br/>pages 361 - 375;<br/>WILLIAM D. STEERS ET AL.: 'Effects of serotonergic<br/>agonists on micturation and sexual function in<br/>the rat'<br/>see abstract</p> <p>---</p>   | 1-3,8-10              |
| A  | <p>DRUGS FUTURE<br/>vol. 16, no. 11, 1991,<br/>pages 1011 - 1026;<br/>M. TURCONI ET AL: 'Azabicycloalkyl<br/>benzimidazolones: Interaction with serotonergic<br/>5-HT<sub>3</sub> and 5-HT<sub>4</sub> receptors and potential<br/>therapeutic implications'<br/>see the whole document</p> <p>---</p> | 1-10                  |

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

**GB 9202376  
SA 68535**

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
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| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s)     | Publication<br>date  |
|---|---------------------|--------------------------------|----------------------|
| EP-A-0501322                              | 02-09-92            | AU-A- 1209492<br>WO-A- 9214727 | 15-09-92<br>03-09-92 |
| EP-A-0467365                              | 22-01-92            | CA-A- 2044854<br>JP-A- 4234328 | 20-01-92<br>24-08-92 |

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For more details about this annex : see Official Journal of the European Patent Office, No. 12/82

# Pathogenesis and Management of the Irritable Bowel Syndrome

W. Grant Thompson

There is no pathophysiologic marker for the functional gastrointestinal (GI) syndromes. Therefore, we must rely on symptoms for their definition and classification. A series of international working teams [1–3] meeting in Rome developed a classification of these disorders and offered definitions and research criteria for each syndrome (Table 9.1). The irritable bowel syndrome (IBS) is distinct from other functional bowel disorders such as functional constipation and functional diarrhea (Table 9.2). The symptom criteria for the IBS are known as the Rome criteria and are shown in Table 9.3. Subjects with functional bowel symptoms that are insufficient to be classified as the IBS or as one of the other syndromes listed in Table 9.2 are said to have an unspecified functional bowel disorder. These disparate syndromes are likely to have different causes and require different tests and treatments.

**Table 9.1** Definitions. (From Thompson *et al.* [3].)

---

*A functional gastrointestinal disorder*

‘A variable combination of persistent or recurrent gastrointestinal symptoms not explained by structural or biochemical abnormalities. These may include symptoms attributable to the oropharynx, oesophagus, stomach, biliary tree, small or large intestine or anus.’

*A functional bowel disorder*

‘A functional gastrointestinal disorder with symptoms attributable to the mid or lower intestinal tract. The symptoms include abdominal pain, bloating or distension and various symptoms of disordered defecation.’

*The irritable bowel syndrome*

‘A functional bowel disorder in which abdominal pain is associated with defecation or a change in bowel habit, and with features of disordered defecation and with distension.’

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Table 9.2 The functional bowel disorders. (From Thompson *et al.* [3].)

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|    |                                       |
|----|---------------------------------------|
| C  | Functional bowel disorders            |
| C1 | Irritable bowel syndrome              |
| C2 | Functional abdominal bloating         |
| C3 | Functional constipation               |
| C4 | Functional diarrhea                   |
| C5 | Unspecified functional bowel disorder |

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Table 9.3 Symptom criteria for IBS. (From Thompson *et al.* [3].)

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At least 3 months of continuous or recurrent symptoms of:

- abdominal pain or discomfort that is:
  - (a) relieved with defecation, and/or
  - (b) associated with a change in frequency of stool, and/or
  - (c) associated with a change in consistency of stools

and:

- two or more of the following, during at least a quarter of occasions or days:
    - (a) altered stool frequency (defined here as more than three bowel movements per day or less than three per week)
    - (b) altered stool form (lumpy/hard or loose/watery stool)
    - (c) altered stool passage (straining, urgency, or feeling of incomplete evacuation)
    - (d) passage of mucus
    - (e) bloating or feeling of abdominal distention
- 

## Epidemiology

The IBS is very common. We [4] showed it to be present in 14% of British adults. Subsequent studies in the USA [5, 6], France [7], New Zealand [8], Denmark [9], and even China [10] indicate that such a prevalence rate is worldwide. Employing the Rome criteria, Drossman *et al.* [11] found the IBS to be present in 11.6% of respondents in a random sample of more than 8000 USA households. This study and a study [12] done in England indicate that IBS is twice as common in women as in men, but reports [9, 13] conflict as to a decreasing prevalence with age. These figures are sensitive to the definitions of IBS that are employed. In one instance [9], prevalence rates of 5–65% were found using different definitions. In a population survey [14], 38% of individuals who had had IBS by Manning and Rome criteria did not have it when surveyed 1 year later. However, about 9% who did not have IBS initially had acquired it. An even greater turnover was found over 5 years in that 95% had experienced some symptoms during that period [9].

Epidemiologic studies are hampered by a dependence on recall, which is notoriously flawed. For example, almost 40% of 961 adults with a previous fracture on their medical record had forgotten it when questioned 15 years later [15]. Most evidence suggests that IBS is a chronic relapsing disorder that probably occurs in most adults during their lifetime.

Most individuals reporting the IBS in population surveys do not seek medical help. Nevertheless, patients with the IBS constitute about 50% of those seen in Western [16] and Asian [17] clinics. Among Western clinic patients, women outnumber men by 3:1 or 4:1 [18, 19]. Curiously, in India and Sri Lanka, this ratio is reversed [20, 21]. Even though most IBS sufferers in the community do not consult a physician for their symptoms those who do present an important and costly health problem [4]. A management strategy must be developed with these facts in mind. There are indications that IBS patients seen by specialists are a subgroup of the whole, with psychosocial characteristics that are distinct from individuals with the same symptoms who do not seek medical care [22, 23] and probably distinct from IBS patients seen in primary care.

## Prognosis

In terms of life expectancy, the prognosis of IBS is excellent. The symptoms are themselves benign, and there is no evidence that they predispose an individual to any other disorder. However, in terms of cure of symptoms, the outlook is not so good. Many studies [14, 24–28] confirm that despite a variety of treatments, most patients who receive a diagnosis of IBS still have symptoms when interviewed 1–10 years later. Given the fickleness of human memory, it is unlikely that many achieve a complete cure. In one survey [9], only 5% of IBS subjects interviewed at 5 years were completely free of symptoms. On the bright side, very few of these individuals had acquired an organic GI disease, and none seems to represent an original misdiagnosis.

## Pathogenesis

Is IBS 'a qualitative or merely a quantitative departure from the psychophysiological reactions of healthy persons?' Thomas Almy [29].

The cause of IBS has confounded physicians for almost two centuries. Despite much research, we cannot even today offer a convincing explanation. Many hold strong beliefs. Some declare it is caused by something

in the diet. Others cite evidence to suggest that it is an infection, or are convinced that it is a motility disorder. Still others believe that it is due to altered perception, a psychological disorder, psychophysiologic phenomena, or even abnormal illness behavior. Perhaps all of these are true, or none are true, or some are true some of the time. Keep Professor Almy's question in mind. A condition affecting at least 11% of a physically healthy population may be no disease at all. Rather, the IBS may represent a normal response of the gut to its environment, made more or less prominent in an individual's consciousness by his or her fears or psychological state.

### **A dietary disorder?**

Burkitt and his medical missionary colleagues [30] in East Africa noted that IBS, constipation, and other 'Western' bowel disorders were uncommon in natives consuming an indigenous high-fiber diet. In a 1972 study [30] of rural African and Westernized populations, they noted that the greater the dietary fiber content, the greater the daily stool weight and the shorter the whole-gut transit time. These facts led to the 'fiber hypothesis,' the concept that many diseases of the colon and other organs result from the ingestion of a Western, refined, low-fiber diet. By implication, IBS is one such disease.

Subsequent studies [31] confirm that a high-fiber diet increases stool bulk and shortens gut transit time. Many studies [32] attest to the value of bran, psyllium, and other bulking materials in the treatment of constipation. However, the presence of IBS has not been linked to an individual's fiber intake, and its presence in countries such as China [10] raises doubt that a single dietary factor such as fiber deficiency is at fault. A more telling source of doubt is the lack of success of dietary fiber supplements, such as bran and psyllium, in the treatment of IBS, as measured by double-blind trials [33]. Fiber may be a safe, cheap placebo, but it is not a cure. The fiber story is made even more confusing by the report [34] that among 'healthy' volunteers, an outgoing personality and a positive self-image predict a larger stool output. Nevertheless, there is evidence [35] that if at least 30 g of dietary fiber is taken daily, constipation and some other symptoms may improve.

Some patients are certain that a food substance is the culprit, if only that food could be identified. This pervasive idea has spawned irrational diets that defy science, cause much inconvenience, and even compromise nutrition. A true food allergy, such as to shellfish, affects systems beyond

the gut and is more likely to cause vomiting and diarrhea than IBS symptoms. Nonimmunoglobulin E (IgE)-mediated intolerances to wheat, dairy products, or beef are claimed to cause diarrhea in some cases, but not the IBS as strictly defined. Very few individuals with IBS can be confirmed by double-blind feedings to have a true food sensitivity [36]. It appears that this approach is likely to be useful only if the patient is suffering from diarrhea, but even that is disputed [36].

Certainly, a careful medical history should seek out evidence of lactose intolerance, excessive caffeine intake, use of sorbitol-containing gum, or other drug or dietary habits that may affect the gut [37]. Although a dietary factor may be involved in IBS in some individuals, it is unlikely to be the sole cause.

### **An infection or inflammation?**

The IBS frequently follows an enteric infection [24, 28, 38]. Could IBS be, after all, an infection or an inflammation set up by an infection? Collins [39] suggests that cytokines emitted from submucosal mast cells or other inflammatory cells might cause the motility disturbances thought to occur in the IBS. Ileal mast-cell counts have been found to be greater in IBS patients than in controls [40]. On the other hand, rectal biopsies performed on 89 patients with the IBS as determined by established criteria and examined by blinded pathologists revealed no histologic difference between IBS patients and controls [41].

### **A motility disorder?**

*'[T]he bowels are at one time constipated, at another lax, in the same person. . . . How the disease has two such different symptoms I do not profess to explain. . .'*  
W. Cumming [42].

Cumming's dilemma persists. Colon motility studies [43] in the 1960s suggested that in constipation, the motility index (frequency of contraction multiplied by amplitude of contraction) is increased. This holds up the passage of stool and causes abdominal pain. Conversely, this line of reasoning suggests that in those with diarrhea, the motility index is decreased. Here, the lax sigmoid permits liquid feces to trickle into the rectum, prematurely triggering defecation. But these observations have not turned out to be reliable features of constipation and diarrhea. Furthermore, it is now believed that the proximal colon and the small intestine are also dysfunctional in IBS [44–46]. In the 1970s, investigators

[47] reported that a 3-cycle per minute (cpm) myoelectric rhythm is more common in IBS patients than in controls. However, the specificity of this observation is doubted. Using a different technology, European workers [48] associated the recording of electrical short bursts in the colon with constipation and the lack of these bursts with diarrhea. In the 1980s, attention was drawn to the small bowel, where the secretory and motor responses to stress seem to be different in IBS patients than in normal individuals [44–46]. However, none of these phenomena is sufficiently specific to permit its use as a diagnostic test of IBS, nor indeed do any of them explain how the symptoms are generated.

Balloons inflated sequentially throughout the gut can identify trigger points that reproduce the abdominal pain experienced by most individuals with IBS [49, 50]. Even here, it is not certain to what extent the pain of IBS is a normal perception of abnormal physiology or an abnormal perception of normal physiology [51]. In IBS there is a tendency for both the small and large bowel to overreact to a variety of stimuli, such as drugs, stress, balloon distention, and even eating [47, 52, 53]. The last may represent an exaggerated gastrocolonic response [47]. Abnormalities in gut motility have yet to explain the diverse features of IBS.

### **A perception disorder?**

The failure of motility observations to adequately explain IBS symptoms has led many to study the sensory or afferent connections between the gut and the brain. IBS patients appreciate pain at lower levels of rectal distention than do other individuals [53, 54], but they do not simply have a generalized low threshold for pain. Pain sensitivity as measured during electrocutaneous stimulation was similar in patients with either IBS or Crohn's disease, and both groups were less sensitive than were controls [55]. The autonomic connections between the enteric nervous system (ENS) and the central nervous system (CNS) are well known, and it is of further interest that the vagus and sympathetic nerves carry more afferent than efferent nerve fibers. 5-Hydroxytryptamine-3 (5-HT<sub>3</sub>) and 5-HT<sub>4</sub> receptors may play an important role in transmitting impulses from the ENS to the CNS. Attempts are being made to develop antagonists to these receptors and thereby decrease gut sensitivity.

An individual's experience of pain may be greatly influenced by emotion, memory, culture, and psychosocial situation [56]. It is useful to distinguish acute pain from chronic pain [57]. Acute pain is linked to tissue pathology or organ dysfunction and, in the case of the gut, is

associated with eating, defecation, and vomiting. Chronic pain is continuous and unassociated with physiologic responses to pain, such as sweating and tachycardia. The patient with chronic pain is often depressed, and there may be secondary gain or prior adverse experiences such as sexual abuse and threatening life events.

The perception of pain varies from patient to patient. Acute, function-related pain is primarily sensory or peripheral and may lend itself to treatment with analgesics directed at the organ involved. Chronic pain, which is influenced more by CNS controlling activity, may require treatment directed at behavior that is influenced by emotion or cognition. Drugs such as the tricyclic antidepressants enhance the production of 5-HT and inhibit pain impulses, thereby reducing the perception of noxious stimuli [58]. They may also enhance endorphin release. In contrast, benzodiazepines carry a risk of habituation, and via gamma-aminobutyric acid (GABA) production, they may inhibit the production of 5-HT and increase pain perception [59].

It is not only pain that may be misperceived by patients. They often misinterpret their bowel action as well [60]. Although stool frequency in the population ranges from three movements per week to three per day, many consider variations within this range to be abnormal. Others misinterpret frequent but hard, fragmented, or lumpy stool as diarrhea when, in fact, gut transit is prolonged. Heaton and O'Donnell [61] have termed this 'pseudodiarrhea.' Patients often complain of symptoms such as borborygmi, flatus, and distention, giving little indication that these symptoms are objectively different from those in noncomplainers. Lasser *et al.* [62] found that patients complaining of 'gas' or 'bloating' had no excess intestinal gas.

Clearly, how sensory input is perceived is an important determinant of the IBS. Acute, function-related symptoms need to be treated differently from symptoms that are chronic, continuous, and associated with psychosocial distress [56]. Nonetheless, perception alone does not explain the altered gut function, nor does it seem important in those with IBS symptoms who do not seek medical care.

### **A psychological disorder?**

The notion that IBS symptoms are interrelated with, perhaps even caused by, an individual's psychological state is as old as the concept of IBS itself. Many studies [22, 23, 63, 64] attest that anxiety, depression, and other forms of psychological distress are more likely in IBS patients than in

patients with organic disease. However, the patients in these studies were in a tertiary care setting and thus unlikely to be representative of all persons experiencing IBS symptoms. Whitehead *et al.* [23] and Drossman *et al.* [22] found that the psychosocial makeup of IBS sufferers in the community who do not see doctors is the same as that of normal individuals. It also appears that IBS and psychosocial distress, when they do occur in the same patient, are not necessarily concurrent [65, 66]. In one British clinic, chronic attendees with IBS were compared with newly referred patients [67]. Although psychological morbidity was similar in the two groups, the social consequences in the chronic attendees were more severe. There are no studies of the psychological state of IBS patients seen in primary care, but these patients are likely to represent an intermediate population.

The foregoing data do not support the notion that psychopathology *causes* the IBS. Indeed, antidepressants are most effective in IBS patients without psychopathology [68]. Perhaps a psychopathological condition worsens IBS symptoms or elevates them to the status of a medical problem in a person's consciousness (a perception disorder?). Could psychological distress be a determinant of health-care seeking? For the emotionally troubled person, IBS symptoms provide a socially acceptable vehicle for care.

These arguments are reinforced by observations [69] that IBS patients tend to seek medical care after a stressful or threatening life event. At the simplest level, a man with IBS who has ignored his symptoms for years may become acutely aware of them when a close relative succumbs to cancer. Compared with age- and less sex-matched controls, IBS patients commonly express concerns about cancer to their doctor [70]. Here, treatment is obvious. Reassure the patient that he or she does not have cancer; further treatment is usually unnecessary.

The management of patients whose visits appear to be precipitated by depression, job loss, marital breakup, or other personal catastrophe may be much more complicated. Many tertiary care patients are polysymptomatic, complaining of fatigue and headache [71, 72]. Others have suffered sexual or physical abuse [73]. In such situations, treatment that focuses on the gut symptoms may be misplaced.

### **A psychophysiological disorder?**

It is the common experience that emotion affects gut function. Who has not suffered some gut upset before an exam, a marriage, a death, or

another stressful or emotional event? In the early 1950s, Almy [74] demonstrated that stress could alter gut motility but that the changes were not specific to the stress. One person may have 'butterflies,' another diarrhea, another vomiting, and yet another a migraine. It seems that a given emotion may elicit different responses at different times in different persons. Perhaps these responses can be learned in early childhood [75]. In the IBS the relationship of symptoms to stress is more subtle. Changes in stress may be important. Some even notice that symptoms improve during a crisis, only to return later.

In IBS patients, the gut appears to be more reactive to a variety of stimuli when compared with controls. Drugs [76], hormones [77], food [52], distention [53, 78], and emotional stress [79] elicit exaggerated motor responses. An air insufflation test has been suggested [80] for IBS. Using radiotelemetry equipment, Valori *et al.* [79] observed that motility of the small bowel was altered in a different manner in IBS patients than in controls. He and his colleagues employed such stressors as heavy metal music, nocturnal arousal, and parking in London traffic to challenge the small bowel. It seems certain that stresses may nonspecifically alter gut function, and the alterations seem to be different in IBS patients. What determines these reactions? Are they clues to the cause of IBS, or are they merely epiphenomena?

### **A behavioral disorder?**

Compared with persons with peptic ulcer, those with IBS have more somatic symptoms, view colds and flu more seriously, and consult physicians more frequently for minor complaints [75]. As children, they also were more likely than others to have received gifts or remained home from school when ill. These data support the notions that persons with IBS are prone to chronic illness behavior and that this behavior is learned.

Health-care seeking in the IBS, particularly at tertiary care centers, may be due as much to a person's cultural and psychosocial states as to the IBS symptoms themselves. How else can one explain why women are more likely than men to take their IBS symptoms to a doctor in Western cultures, while the opposite is true in India [4]? Why do only a minority of those with the IBS seek medical attention? The concurrence of threatening life events and psychosocial distress may partially explain these phenomena.

### An integrated view

It must be evident from the foregoing that purely mechanistic or purely psychological explanations of IBS are inadequate reconciliations of the available facts. The physician should weigh all the considerations presented here as he or she interviews a patient (Figure 9.1). Evaluation of the relative importance of diet, disordered physiology, misperceptions, psychosocial maladaptations, and altered behavior in a patient may be as important to management as the establishment of a correct diagnosis. Past experience with diagnosing and treating peptic ulcers should make us cautious about accepting any of the current hypotheses. There, the focus on either acid secretion or psychosomatics as the cause blinded us to other possibilities and made it difficult to accept the role of *Helicobacter pylori*.

Noone's gut functions perfectly all the time, and variation in the population is great. Whatever the underlying pathophysiology, some people ignore the symptoms, while others permit the symptoms to dominate their lives. This variability is undoubtedly influenced by the emotions and life events that buffet us all. Further complicating the matter are human behavior, subtly learned in early childhood, and the negative incentives of Western social welfare systems. Since cure is elusive and we can do little to change life situations, the objective of IBS treatment should be improved functioning.

### A therapeutic approach

Despite the reality that the pathogenesis of IBS is unknown, we have learned much about its epidemiology, prognosis, and diagnosis. The task

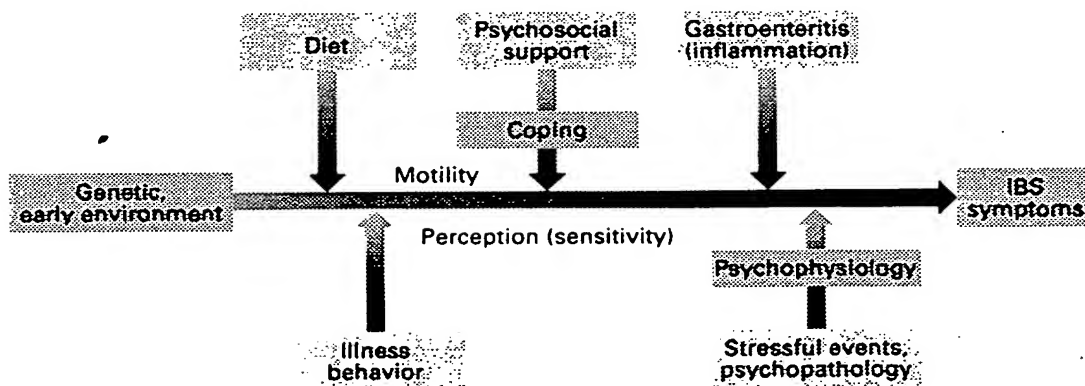


Fig. 9.1 Pathogenesis of IBS.

is to develop a strategy of management based on the known facts. Such a strategy should rely on six principles:

- 1 a positive diagnosis;
- 2 consideration of the patient's agenda;
- 3 critical appraisal of drugs and placebos;
- 4 the use of dietary fiber;
- 5 continuing care;
- 6 a graded therapeutic response.

### **A positive diagnosis**

A careful history and physical examination permit a confident diagnosis that stands up over time. Physicians who consider the IBS a diagnosis of exclusion feel compelled to exclude all organic disease. This approach is expensive, especially if extrapolated to the many patients who seek medical care. The physician should attempt to establish a positive diagnosis at the first clinical encounter [3, 37, 56]. This is usually possible using the criteria shown in Table 9.3. A condition that affects up to 20% of the population is bound to coexist with organic disease in some. Therefore, one should inquire about symptoms such as anemia, bleeding, fever, weight loss, or a recent change in bowel habit.

If such symptoms and physical findings are absent, the investigation should be minimal. A sigmoidoscopy should be performed, but biopsy in search of microscopic colitis in the absence of continuous diarrhea is an unnecessary expense [41]. If the patient is older than 40 years of age or has risk factors for colon carcinoma, a barium enema is prudent. Even though the symptoms of the IBS are not those of polyp or cancer, a 'clean colon' is a reassuring start for all concerned. Other tests should be avoided unless indicated. An early, confident diagnosis permits tests to be minimized and reassures the patient that there is no mortal disease. Especially since fear of cancer is so common among IBS patients [70], such reassurance may be the physician's most effective therapeutic weapon.

### **The patient's agenda**

Most persons with the IBS do not consult doctors. Those who do may have reasons for the visit beyond the gut. Severity of symptoms may be important, but psychosocial factors must also affect the decision. The answer to the question 'Why has this patient come to see the doctor now?' may be an important therapeutic clue. Fear of serious disease should be

met by firm reassurance that none exists. Threatening life events, whether they precipitate the IBS or the consultation, should be discussed. Some patients may require psychological help or stress management expertise, but simple supportive psychotherapy by the attending physician may be salutary. In a Swedish study [81], IBS patients treated with eight sessions of supportive psychotherapy, which could be performed in any physician's office, had fewer symptoms and less psychological and physical disability, compared to a control group, when they were seen 3 months later. The improvement was even more marked 1 year later. This supports the notion that early, careful attention to the patient's psychosocial concerns has effective and lasting benefit. Such an approach is supported by an English study [82], which also noted that improvement is most likely if psychopathology is recognized and dealt with and the pain is not constant.

### Drugs and placebos

*'[N]ot a single study has been published that provides compelling evidence that any therapeutic agent is efficacious in the global treatment of IBS.'* K.B. Klein [83].

There are too many clinical trials of drugs in IBS to report here. The reader is referred to Klein [83], who reviewed controlled trials conducted over a 20-year period and found them all flawed. The entry criteria are usually unclear, and the symptom criteria of Manning [84], Kruis [85], and the Rome teams [3] are recent innovations. Many studies are too small or too short, or have too many dropouts. Others have an inappropriate trial design or use improper statistics. Thus, no drug has been proven to be globally effective in treating IBS.

Although trial methodology is improving, studies subsequent to Klein's critique are still inadequate. An international working team [86] agreed with and updated Klein's conclusions and set out suggested standards for clinical trials. One meta-analysis [87] examined randomized controlled trials of smooth-muscle relaxants and concluded that five such drugs showed 27% and 19% improvements over placebo in global assessment and pain, respectively. However, only 26 of 148 known trials were selected, and abstracts and letters were discarded. Since it is likely that some trials failed to appear at all, a publication bias must be suspected. Even with negative studies possibly excluded, the benefits seem marginal at most. IBS is a benign disorder that affects up to 20% of adults through long periods of their lives. Physicians should discourage the

chronic use of costly, systemic drugs of doubtful benefit, which in some cases may have unwanted consequences that can be more troublesome than the IBS itself.

Nevertheless, amid the rigors of science, there is a place for common sense in the use of drugs to treat the symptoms of IBS (Table 9.4). If diarrhea is the dominant symptom, with urgency, even incontinence, loperamide (Imodium®) may be helpful. This drug not only slows gut motility and decreases small bowel secretion but also increases anal sphincter strength [88]. Unlike other opiates, it does not enter the brain. Provided the diarrhea is genuine and not pseudodiarrhea [61], and reactive constipation does not result, such a drug can target the most troublesome symptom for a few patients. Other examples of such targeted therapy include bran or psyllium for constipation [33], avoidance of vegetables in the cabbage family, and perhaps use of alpha-D-galactosidase (Beano®) for excessive flatus, and a preprandial anticholinergic agent for abdominal pain that occurs after meals [47].

Anxiety and depression must be treated on their own merits. Treatment of psychological distress may permit a patient to cope better with IBS symptoms. In some pain-dominant IBS patients, tricyclic antidepressants may be helpful even if depression is not obvious [65, 66, 89]. These drugs have proven effective in other chronic pain syndromes [90] and may act via central pathways that influence the perception of pain. They seem to be effective at low doses and before any change in mood

Table 9.4 Drugs useful for certain difficult IBS symptoms. (From Thompson [37].)

| Indication  | Drug  | Maximum dose   |
|---|---|--|
| Diarrhea-dominant IBS   | Loperamide (Imodium®)<br>Cholestyramine (Questran®) | 1–2 tablets three times daily<br>1 teaspoonful (4 g) three times daily |
| Pain-dominant IBS<br>Postmeal pain [47]<br>Chronic pain syndrome [68] | Dicyclomine (Bentyl®)<br>Amitriptyline (Elavil®)    | 10–20 mg before meals<br>25 mg at bedtime, with increments to 100 mg   |
| Constipation  | Bran or psyllium                                    | 1 tablespoonful three times daily with meals, and adjust               |
| Gas/bloat/flatus  | Alpha-D-galactosidase (Beano®)<br>Simethicone       | —<br>1–2 tablets three times daily                                     |

occurs. A recommended starting dose of amitriptyline (Elavil<sup>®</sup>) is 25 mg at bedtime, with increments every 4–5 days until benefit is achieved. The dose seldom exceeds 100 mg, but anticholinergic or sedating side effects may necessitate switching to another drug, such as doxepin (Sinequan<sup>®</sup>).

An important feature of IBS symptoms is the tendency to improve with placebo. In existing therapeutic trials, the placebo response ranges from 40 to 70% [37]. There are lessons to be learned from this placebo response.

- 1 It demonstrates the variability of the disease, which tends to improve with time.
- 2 It supports the contention that no drug is generally acceptable for IBS patients without convincing demonstration of efficacy in defined-entry, randomized, placebo-controlled, double-blind clinical trials.
- 3 Placebos may be useful in certain circumstances. It is said that if a placebo is to have a therapeutic effect, the patient must believe that it will. Nevertheless, in a group of neurotic patients, placebo was effective even when they knew the pills were inert [91]. It seems that the symbolic giving of medication has a therapeutic value. Logical placebos that have a plausible rationale, yet are inexpensive and safe, may exploit these phenomena.
- 4 The most important implication of the placebo response is that it demonstrates the beneficial effect of a successful physician–patient encounter.

### Dietary fiber

Although bran, psyllium, and dietary fiber are not proven effective in the treatment of IBS [33, 92, 93], they should still be tried by the primary care doctor. Fiber is effective in constipation and pseudodiarrhea. Ingestion of sufficient fiber has a visible effect on stool form and is a cheap, safe method of eliciting the placebo response. It also involves the patient in his or her own care in a way that passive ingestion of a pill may not. Fiber needs to be taken in sufficient doses. To encourage compliance and more easily titrate the dose of fiber, the author prefers to have the patient take three tablespoonsful three times a day with meals and adjust the amount according to its effect on the stool. There are reports of intolerance to bran in patients at tertiary care centers, but such patients have usually tried bran and failed [94, 95]. Specialists are less likely to achieve success with fiber in their selected patients than a primary care physician encountering a patient for the first time. If bran works, referral becomes redundant.

### Continuing care

Cure, or even acceptance of the diagnosis, is an unrealistic goal for some troubled IBS patients. Unsatisfied with their doctor, they are prone to turn to practitioners of alternative medicine [96, 97]. Some diets and remedies recommended by these sources are inappropriate, even harmful, and important intervening disease may be overlooked. It is, therefore, important that the physician assure the patient of the availability of continuing care.

Emotionally disturbed patients benefit from regular, brief visits. These visits offer reassurance, and control 'doctor-shopping' and inappropriate ordering of tests and treatments. Through such visits, the doctor can be vigilant for a change in symptoms. Assistance may be sought from psychologists, psychiatrists, or other services if needed. Some patients may benefit from a stress management program. Patients with severe symptoms may require the multidisciplinary services of a pain clinic. Although biofeedback [98] and hypnosis [99] seem to benefit some patients, such services are not available in many cities. If the physician seems to lose the confidence of a patient, referral to an esteemed colleague may help by confirming the diagnosis and reinforcing the management plan.

### A graded therapeutic response [56]

The therapeutic response must be tailored to the individual needs of IBS sufferers if we are to use our resources economically and effectively. Most individuals with the IBS do not seek medical attention. Many who do consult a primary care physician are worried about the meaning of their symptoms and will likely respond to explanation and reassurance. Those who return with the same symptoms or who are referred to specialists may require more attention. Those who chronically seek help from subspecialists are a small, unhappy, but costly subgroup in whom psychosocial factors may be more disabling than the gut symptoms themselves.

The primary care physician should emphasize the positive diagnosis, the chronic yet benign nature of the symptoms, the role of stress, and the inutility of drugs. Bulk, such as bran, improves constipation and is otherwise a safe, cheap placebo. For nonresponders, once the foregoing items have been dealt with satisfactorily, supportive psychotherapy and drugs for specific indications may be added. Overinvestigation or repeated testing and referral without substantial indication may undermine the patient's confidence in the doctor's conclusions. The emphasis should

be directed toward improved daily functioning. There may be a role for special treatments such as stress management, psychotherapy, behavioral modification, or a psychotherapeutic agent such as amitriptyline. In the end, there is no substitute for the ongoing support of a caring family doctor.

## Summary

The cause of the IBS is unknown, but it is very common in the community. Most sufferers do not see doctors. There is evidence that factors other than symptoms contribute to the decision to seek medical care. Examination of these factors not only suggests that the cause is multifactorial, but also offers clues for the management of individual patients. There is either some evidence for, or strong belief in, the importance of diet, inflammation, disordered motility, psychophysiology, or psychopathology in the genesis of the IBS. It seems that severe life events and an altered perception of symptoms may also be important and that several factors may act in concert to induce illness behavior. In some patients, all factors may be present; in others, apparently none. But the more factors are at work, the more complex the treatment.

Management should take advantage of the known features of the disease. Its prevalence, recognizable symptoms, and benign nature indicate the reassurance value of a positive diagnosis. The tendency of patients, especially chronic complainers, to have psychopathology or antecedent stressful life events may indicate important management issues. Although drugs are unproved in the global treatment of IBS, certain agents may benefit specific symptoms and may also employ the placebo response to advantage. Insecure patients or chronic complainers need continuing care. Different levels of disability require a graded treatment response to IBS complaints. This implies reassurance and drug-free management at the primary care level, with increments of psychosocial support and specific use of drugs in nonresponders. The goal of therapy in severe, intractable cases should be improved functioning rather than cure.

## References

- 1 Drossman DA, Funch-Jensen P, Janssens J, Talley NJ, Thompson WG, Whitehead WE. Identification of subgroups of functional bowel disorders. *Gastroenterol Int* 1990;3:159-72.

- 2 Thompson WG, Working Team for Functional Bowel Disorders. C. Functional bowel disorders and D. functional abdominal pain. In: Drossman DA, ed. *The Functional Gastrointestinal Disorders*. Boston: Little, Brown, 1994:115-73.
- 3 Thompson WG, Creed F, Drossman DA, Heaton KW, Mazzacca G. Functional bowel disorders and functional abdominal pain. *Gastroenterol Int* 1992;5:75-91.
- 4 Thompson WG. Irritable bowel syndrome: prevalence, prognosis and consequences. *Can Med Assoc J* 1986;134:111-13.
- 5 Drossman DA, Sandler RS, McKee DC, Lovitz AJ. Bowel patterns among subjects not seeking health care: use of a questionnaire to identify a population with bowel dysfunction. *Gastroenterology* 1982;83:529-34.
- 6 Longstreth GF, Wolde-Tsadik G. Irritable bowel-type symptoms in HMO examinees: prevalence, demographics and clinical correlates. *Dig Dis Sci* 1993;38:1581-9.
- 7 Bommelaer G, Rouch M, Dapoigny M *et al.* Epidemiology of intestinal functional disorders in an apparently healthy population. *Gastroenterol Clin Biol* 1986;10:7-12.
- 8 Welch GW, Pomare EW. Functional gastrointestinal symptoms in a Wellington community sample. *N Z Med J* 1990;103:418-20.
- 9 Kay L, Jørgensen T, Jensen KH. The epidemiology of irritable bowel syndrome in a random population: prevalence, incidence, natural history and risk factors. *J Intern Med* 1994;236:23-30.
- 10 Wen B-Z, Pan Q-Y. Functional bowel disorders in apparently healthy Chinese people. *Chin J Epidemiol* 1988;9:345-9.
- 11 Drossman DA, Li Z, Andruzzi E *et al.* US householder survey of functional gastrointestinal disorders: prevalence, sociodemography and health impact. *Dig Dis Sci* 1993;38:1569-80.
- 12 Heaton KW, O'Donnell LJD, Bradden FEM, Mountford RA, Hughes AO, Cripps PJ. Symptoms of irritable bowel syndrome in a British urban community: consulters and nonconsulters. *Gastroenterology* 1992;102:1962-7.
- 13 Argreus L, Svardsudd K, Nyren O, Tibblin G. The epidemiology of abdominal symptoms: prevalence and demographic characteristics in a Swedish adult population: a report from the Abdominal Symptom Study. *Scand J Gastroenterol* 1994;29:102-9.
- 14 Talley NJ, Weaver AL, Zinsmeister AR, Melton LJ III. Onset and disappearance of gastrointestinal symptoms and functional gastrointestinal disorders. *Am J Epidemiol* 1992;136:165-77.
- 15 Jonsson B, Gardsell P, Johnell O, Redlund-Johnell I, Sernbo I. Remembering fractures: fracture registration and proband recall. *J Epidemiol Community Health* 1995;48:489-90.
- 16 Switz DM. What the gastroenterologist does all day: a survey of a state society's practice. *Gastroenterology* 1976;70:1048-50.
- 17 Kang JY, Yap I, Gwee KA. The pattern of functional and organic disorders in an Asian gastroenterological clinic. *J Gastroenterol Hepatol* 1994;9:124-7.
- 18 Thompson WG. Gastrointestinal symptoms in the irritable bowel compared with peptic ulcer and inflammatory bowel disease. *Gut* 1984;25:1089-92.
- 19 Harvey RF, Salih SY, Read AE. Organic and functional disorders in 2000 gastroenterology outpatients. *Lancet* 1983;1:632-4.
- 20 Mendis BLJ, Wijesiriwardena BC, Sheriff MHR, Dharmadasa K. Irritable bowel syndrome. *Ceylon Med J* 1982;27:171-81.
- 21 Mathur AK, Tandon BN, Prakash OM. Irritable colon syndrome. *J Indian Med Assoc* 1966;46:651-5.

- 2 Thompson WG, Working Team for Functional Bowel Disorders. C. Functional bowel disorders and D. functional abdominal pain. In: Drossman DA, ed. *The Functional Gastrointestinal Disorders*. Boston: Little, Brown, 1994:115-73.
- 3 Thompson WG, Creed F, Drossman DA, Heaton KW, Mazzacca G. Functional bowel disorders and functional abdominal pain. *Gastroenterol Int* 1992;5:75-91.
- 4 Thompson WG. Irritable bowel syndrome: prevalence, prognosis and consequences. *Can Med Assoc J* 1986;134:111-13.
- 5 Drossman DA, Sandler RS, McKee DC, Lovitz AJ. Bowel patterns among subjects not seeking health care: use of a questionnaire to identify a population with bowel dysfunction. *Gastroenterology* 1982;83:529-34.
- 6 Longstreth GF, Wolde-Tsadik G. Irritable bowel-type symptoms in HMO examinees: prevalence, demographics and clinical correlates. *Dig Dis Sci* 1993;38:1581-9.
- 7 Bommelaer G, Rouch M, Dapoigny M *et al*. Epidemiology of intestinal functional disorders in an apparently healthy population. *Gastroenterol Clin Biol* 1986;10:7-12.
- 8 Welch GW, Pomare EW. Functional gastrointestinal symptoms in a Wellington community sample. *N Z Med J* 1990;103:418-20.
- 9 Kay L, Jørgensen T, Jensen KH. The epidemiology of irritable bowel syndrome in a random population: prevalence, incidence, natural history and risk factors. *J Intern Med* 1994;236:23-30.
- 10 Wen B-Z, Pan Q-Y. Functional bowel disorders in apparently healthy Chinese people. *Chin J Epidemiol* 1988;9:345-9.
- 11 Drossman DA, Li Z, Andruzzi E *et al*. US householder survey of functional gastrointestinal disorders: prevalence, sociodemography and health impact. *Dig Dis Sci* 1993;38:1569-80.
- 12 Heaton KW, O'Donnell LJD, Bradden FEM, Mountford RA, Hughes AO, Cripps PJ. Symptoms of irritable bowel syndrome in a British urban community: consulters and nonconsulters. *Gastroenterology* 1992;102:1962-7.
- 13 Argreus L, Svardsudd K, Nyren O, Tibblin G. The epidemiology of abdominal symptoms: prevalence and demographic characteristics in a Swedish adult population: a report from the Abdominal Symptom Study. *Scand J Gastroenterol* 1994;29:102-9.
- 14 Talley NJ, Weaver AL, Zinsmeister AR, Melton LJ III. Onset and disappearance of gastrointestinal symptoms and functional gastrointestinal disorders. *Am J Epidemiol* 1992;136:165-77.
- 15 Jonsson B, Gardsell P, Johnell O, Redlund-Johnell I, Sernbo I. Remembering fractures: fracture registration and proband recall. *J Epidemiol Community Health* 1995;48:489-90.
- 16 Switz DM. What the gastroenterologist does all day: a survey of a state society's practice. *Gastroenterology* 1976;70:1048-50.
- 17 Kang JY, Yap I, Gwee KA. The pattern of functional and organic disorders in an Asian gastroenterological clinic. *J Gastroenterol Hepatol* 1994;9:124-7.
- 18 Thompson WG. Gastrointestinal symptoms in the irritable bowel compared with peptic ulcer and inflammatory bowel disease. *Gut* 1984;25:1089-92.
- 19 Harvey RF, Salih SY, Read AE. Organic and functional disorders in 2000 gastroenterology outpatients. *Lancet* 1983;1:632-4.
- 20 Mendis BLJ, Wijesiriwardena BC, Sheriff MHR, Dharmadasa K. Irritable bowel syndrome. *Ceylon Med J* 1982;27:171-81.
- 21 Mathur AK, Tandon BN, Prakash OM. Irritable colon syndrome. *J Indian Med Assoc* 1966;46:651-5.

- 22 Drossman DA, McKee DC, Sandler RS *et al.* Psychosocial factors in the irritable bowel syndrome: a multivariate study of patients and nonpatients with irritable bowel syndrome. *Gastroenterology* 1988;95:701-8.
- 23 Whitehead WE, Bosmajian L, Zonderman AB, Costa PT Jr, Schuster MM. Symptoms of psychologic distress associated with irritable bowel syndrome: comparison of community and medical clinic samples. *Gastroenterology* 1988;95:709-14.
- 24 Chaudhary NA, Truelove SC. The irritable colon syndrome. *Q J Med* 1962;31:307-22.
- 25 Waller SL, Misiewicz JJ. Prognosis in the irritable-bowel syndrome. *Lancet* 1969;2:753-6.
- 26 Holmes KM, Salter RH. Irritable bowel syndrome: a safe diagnosis. *BMJ* 1982;285:1533-4.
- 27 Svendsen JH, Munck LK, Andersen JR. Irritable bowel syndrome — prognosis and diagnostic safety: a 5-year follow-up study. *Scand J Gastroenterol* 1985;20:415-18.
- 28 Harvey RF, Mauad EC, Brown AM. Prognosis in the irritable bowel syndrome: a five-year prospective study. *Lancet* 1987;1:963-5.
- 29 Almy TP. The irritable bowel syndrome: back to square one? *Dig Dis Sci* 1980;25:401-3.
- 30 Burkitt DP, Walker ARP, Painter NS. Effect of dietary fibre on stools and transit times, and its role in the causation of disease. *Lancet* 1972;2:1408-12.
- 31 Müller-Lissner SA. Effect of wheat bran on weight of stool and gastrointestinal transit time: a meta analysis. *BMJ* 1988;296:615-17.
- 32 Taylor R. Management of constipation, I: high fibre diets work. *BMJ* 1900;300:1063-4.
- 33 Heaton KW. Role of dietary fibre in irritable bowel syndrome. In: Read NW, ed. *Irritable Bowel Syndrome*. London: Grune & Stratton Ltd, 1985:203-22.
- 34 Tucker DM, Sandstead HH, Logan GM Jr *et al.* Dietary fiber and personality factors as determinants of stool output. *Gastroenterology* 1981;81:879-83.
- 35 Lambert JP, Brunt PW, Mowat NAG *et al.* The value of prescribed 'high-fibre' diets for the treatment of the irritable bowel syndrome. *Eur J Clin Nutr* 1991;45:601-9.
- 36 Pearson DJ. Pseudo food allergy. *BMJ* 1986;292:221-2.
- 37 Thompson WG. *Gut Reactions*. New York: Plenum Medical Book Co, 1989.
- 38 White WH. A study of 60 cases of membranous colitis. *Lancet* 1905;2:1229-35.
- 39 Collins SM. Is the irritable gut an inflamed gut? *Scand J Gastroenterol* 1992;192(Suppl.):102-5.
- 40 Weston AP, Biddle WL, Bhatia PS, Miner PB Jr. Terminal ileal mucosal mast cells in irritable bowel syndrome. *Dig Dis Sci* 1993;38:1590-5.
- 41 McIntosh D, Thompson WG, Patel D, Barr JR, Guindi M. Is rectal biopsy necessary in irritable bowel syndrome? *Am J Gastroenterol* 1992;87:1407-9.
- 42 Cumming W. Electro-galvanism in a peculiar affection of the mucous membrane of the bowels. *Lond Med Gazette* 1849;NS9:969-73.
- 43 Connell AM. The motility of the pelvic colon, II: paradoxical motility in diarrhoea and constipation. *Gut* 1962;3:342-8.
- 44 Kellow JE, Phillips SF. Altered small bowel motility in irritable bowel syndrome is correlated with symptoms. *Gastroenterology* 1987;92:1885-93.
- 45 Kellow JE, Phillips SF, Miller LJ, Zinsmeister AR. Dysmotility of the small intestine in irritable bowel syndrome. *Gut* 1988;29:1236-43.
- 46 Kumar D, Wingate DL. The irritable bowel syndrome: a paroxysmal motor disorder. *Lancet* 1985;2:973-7.
- 47 Sullivan MA, Cohen S, Snape WJ Jr. Colonic myoelectrical activity in irritable-bowel syndrome: effect of eating and anticholinergics. *N Engl J Med* 1978;298:878-83.

- 48 Bueno L, Fioramonti J, Ruckebusch Y, Frexinos J, Coulom P. Evaluation of colonic myoelectrical activity in health and functional disorders. *Gut* 1980;21:480-5.
- 49 Swarbrick ET, Hegarty JE, Bat L, Williams CB, Dawson AM. Site of pain from the irritable bowel. *Lancet* 1980;2:443-6.
- 50 Moriarty KJ, Dawson AM. Functional abdominal pain: further evidence that whole gut is affected *BMJ* 1982;284:1670-2.
- 51 Ford MJ. The irritable bowel syndrome. *J Psychosom Res* 1986;30:399-410.
- 52 Wright SH, Snape WJ Jr, Battle W, Cohen S, London RL. Effect of dietary components on gastrocolonic response. *Am J Physiol* 1980;238:G228-32.
- 53 Whitehead WE, Holtkotter B, Enck P *et al.* Tolerance for rectosigmoid distention in irritable bowel syndrome. *Gastroenterology* 1990;98:1187-92.
- 54 Ritchie J. Pain from distension of the pelvic colon by inflating a balloon in the irritable bowel syndrome. *Gut* 1973;14:125-32.
- 55 Cook IJ, van Eeden A, Collins SM. Patients with irritable bowel syndrome have greater pain tolerance than normal subjects. *Gastroenterology* 1987;93:727-33.
- 56 Drossman DA, Thompson WG. The irritable bowel syndrome: review and a graduated multicomponent treatment approach. *Ann Intern Med* 1992;116:1009-16.
- 57 Buccini R, Drossman DA. Chronic idiopathic abdominal pain. *Curr Concepts Gastroenterol* 1988;12:3-11.
- 58 Peters JL, Large RG. A randomised control trial evaluating in- and outpatient pain management programmes. *Pain* 1990;41:283-93.
- 59 Melzack R, Wall P. Gate-control and other mechanisms. In: Melzack R, Wall P, eds. *The Challenge of Pain*, 2nd edn. London: Pelican Books, 1988:165-93.
- 60 O'Donnell LJD, Virjee J, Heaton KW. Detection of pseudodiarrhoea by simple clinical assessment of intestinal transit rate. *BMJ* 1990;300:439-40.
- 61 Heaton KW, O'Donnell LJD. An office guide to whole gut transit time: patients' recollection of their stool form. *J Clin Gastroenterol* 1994;19:28-30.
- 62 Lasser RB, Bond JH, Levitt MD. The role of intestinal gas in functional abdominal pain. *N Engl J Med* 1975;293:524-6.
- 63 Hislop IG. Psychological significance of the irritable colon syndrome. *Gut* 1971;12:452-7.
- 64 Clouse RE. Anxiety and gastrointestinal illness. *Psychiatr Clin North Am* 1988;11:399-417.
- 65 Clouse RE, Lustman PJ, Geisman RA, Alpers DH. Antidepressant therapy in 138 patients with irritable bowel syndrome: a five-year clinical experience. *Aliment Pharmacol Ther* 1994;8:409-16.
- 66 Walker EA, Roy-Byrne PP, Katon WJ. Irritable bowel syndrome and psychiatric illness. *Am J Psychiatry* 1990;147:567-72.
- 67 Guthrie EA, Creed FH, Whorwell PJ, Tomenson B. Outpatients with irritable bowel syndrome: a comparison of first time and chronic attenders. *Gut* 1992;33:361-3.
- 68 Clouse RE. Antidepressants for functional gastrointestinal syndromes. *Dig Dis Sci* 1994;39:2352-63.
- 69 Creed F, Craig T, Farmer R. Functional abdominal pain, psychiatric illness, and life events. *Gut* 1988;29:235-42.
- 70 Kettell J, Jones R, Lydeard S. Reasons for consultation in irritable bowel syndrome: symptoms and patient characteristics. *Br J Gen Pract* 1992;42:459-61.
- 71 Whorwell PJ, McCallum M, Creed FH, Roberts CT. Non-colonic features of irritable bowel syndrome. *Gut* 1986;27:37-40.
- 72 Maxton DG, Morris JA, Whorwell PJ. Ranking of symptoms by patients with the irritable bowel syndrome. *BMJ* 1989;299:1138.

- 73 Drossman DA, Leserman J, Nachman G *et al.* Sexual and physical abuse in women with functional or organic gastrointestinal disorders. *Ann Intern Med* 1990;113:828-33.
- 74 Almy TP. Experimental studies on the irritable colon. *Am J Med* 1951;10:60-7.
- 75 Whitehead WE, Winget C, Fedoravicius AS, Wooley S, Blackwell B. Learned illness behavior in patients with irritable bowel syndrome and peptic ulcer. *Dig Dis Sci* 1982;27:202-8.
- 76 Wangel AG, Deller DJ. Intestinal motility in man, III: mechanisms of constipation and diarrhea with particular reference to the irritable colon syndrome. *Gastroenterology* 1965;48:69-84.
- 77 Harvey RF, Read AE. Effect of cholecystokinin on colon motility and symptoms in patients with the irritable bowel syndrome. *Lancet* 1973;1:1-3.
- 78 Bradette M, Delvaux M, Staumont G, Fioramonti J, Bueno L, Flexinos J. Evaluation of colonic sensory thresholds in IBS patients using a barostat: definition of optimal conditions and comparison with healthy subjects. *Dig Dis Sci* 1994;39:449-57.
- 79 Valori RM, Kumar D, Wingate DL. Effects of different types of stress and of 'prokinetic' drugs on the control of the fasting motor complex in humans. *Gastroenterology* 1986;90:1890-900.
- 80 Kang JY, Gwee KA, Yap I. The colonic air insufflation test indicates a colonic cause of abdominal pain: an aid in the management of irritable bowel syndrome. *J Clin Gastroenterol* 1994;18:19-22.
- 81 Svedlund J, Sjödin I, Ottosson J-O, Dotevall G. Controlled study of psychotherapy in irritable bowel syndrome. *Lancet* 1983;2:589-92.
- 82 Guthrie E, Creed F, Dawson D, Tomenson B. A controlled trial of psychological treatment for the irritable bowel syndrome. *Gastroenterology* 1991;100:450-7.
- 83 Klein KB. Controlled treatment trials in the irritable bowel syndrome: a critique. *Gastroenterology* 1988;95:232-41.
- 84 Manning AP, Thompson WG, Heaton KW, Morris AF. Towards positive diagnosis of the irritable bowel. *BMJ* 1978;2:653-4.
- 85 Kruis W, Thieme CH, Weinzierl M, Schussler P, Holl J, Paulus W. A diagnostic score for the irritable bowel syndrome: its value in the exclusion of organic disease. *Gastroenterology* 1984;87:1-7.
- 86 Talley NJ, Nyren O, Drossman DA *et al.* The irritable bowel syndrome: toward optimal design of controlled treatment trials. *Gastroenterol Int* 1994;6:189-211.
- 87 Poynard T, Naveau S, Mory B, Chaput JC. Meta-analysis of smooth muscle relaxants in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 1994;8:499-510.
- 88 Read M, Read NW. Anal sphincter function in diarrhoea: influence of loperamide. *Clin Res Rev* 1981;1:219-24.
- 89 Lancaster-Smith MJ, Prout BJ, Pinto T, Anderson JA, Schiff AA. Influence of drug treatment on the irritable bowel syndrome and its interaction with psychoneurotic morbidity. *Acta Psychiatr Scand* 1982;66:33-41.
- 90 Tura B, Tura SM. The analgesic effect of tricyclic antidepressants. *Brain Res* 1990;518:19-22.
- 91 Brody H. The lie that heals: the ethics of giving placebos. *Ann Intern Med* 1982;97:112-18.
- 92 Heaton KW. Effect of diet on intestinal function and dysfunction. In: Snape WJ Jr, ed. *Pathogenesis of Functional Bowel Disease*. New York: Plenum Medical Book Co, 1989:79-99.
- 93 Snook J, Shepherd HA. Bran supplementation in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther* 1994;8:511-14.

- 94 Francis CY, Whorwell PJ. Bran and irritable bowel syndrome: time for reappraisal. *Lancet* 1994;344:39-40.
- 95 Thompson WG. Doubts about bran. *Lancet* 1994;344:3.
- 96 Smart HL, Mayberry JF, Atkinson M. Alternative medicine consultations and remedies in patients with the irritable bowel syndrome. *Gut* 1986;27:826-8.
- 97 Verhoef MJ, Sutherland LR, Brkich L. Use of alternative medicine by patients attending a gastroenterology clinic. *Can Med Assoc J* 1990;142:121-5.
- 98 Schwarz SP, Blanchard EB, Neff DF. Behavioral treatment of irritable bowel syndrome: a 1-year follow-up study. *Biofeedback Self Regul* 1986;11:189-98.
- 99 Whorwell PJ, Prior A, Colgan SM. Hypnotherapy in severe irritable bowel syndrome: further experience. *Gut* 1987;28:423-5.